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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1614	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/814,199	CARBONI ET AL.	
	Examiner	Art Unit	
	ZOHREH VAKILI	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *2-20 and 23-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,21,22 and 26-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/7/2004 and 4/3/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-30 are presented for examination.

Applicant's response to the election/restriction requirement filed on January 2, 2008 is acknowledged. Accordingly, Applicant elects The IGF1R inhibitor species without traverse.

Claims 1, 21, 22 and 26-30 encompass the elected invention and are herein examined on the merits. Claims 2-20 and 23-25 are withdrawn from consideration as being directed to non-elected subject matter.

Claim Rejections - 35 USC § 112 (2nd Paragraph)

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 21-22, and 26-30 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites the administration of "an effective amount" of an IGF1R inhibitor. This limitation is indefinite because it is not clear what the amount being administered is effective for. The preamble of the claim is not linked to the body of the claim in such a way as to clearly convey that the "effective amount" being administered is effective to treat the condition recited in the preamble. The phrase "an effective amount" has been held to be

indefinite when the claim fails to state the function which is to be achieved and more than one effect can be implied from the specification or the relevant art. *In re Fredericksen* 213 F.2d 547, 102 USPQ 35 (CCPA 1954). In this case, an effective amount of an inhibitor of IGF1R could reasonably be an amount that simply inhibits IGF1R. However, this amount does not, *a priori*, correlate with an amount effective to treat tumors as recited in the instant claims.

Accordingly, for the above reasons, the claims are deemed properly rejected.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 21-22, and 26-30 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an Enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims.

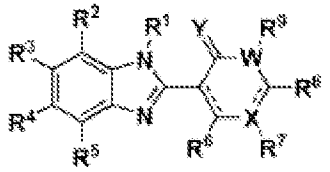
These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping

[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to treating a mammal having cancer comprising administering an effective amount an IGF1R inhibitor in combination with an anticancer agent, wherein the IGF1R inhibitor has the formula I:



I

X is N, C or a direct bond;

Y is O or S;

W is N, C, O, or S; provided that if W is O or S, R^3 is absent;

R^1 is H, alkyl, or alkoxy;

R^2 and R^4 are independently H or alkyl;

R^3 is H, C_{1-6} alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, halo, amino, $-OR^{60}$, $-NO_2$, -OH, $-SR^{60}$, $-NR^{60}R^{61}$, -CN, $-C(O)R^{60}$, $-CO_2R^{60}$, $-CONR^{60}R^{61}$, $OCONR^{60}R^{61}$, $-NR^{62}CONR^{60}R^{61}$, $-NR^{60}SO_2R^{61}$, $-SO_2NR^{60}R^{61}$, $-SO_2R^{63}$, $-C(NR^{62})NR^{60}R^{61}$, $-C(NH^{62})$-morpholine, aryl, heteroaryl, $-(CH_2)_nC(O)_2-R^{60}$, $-NR^{60}R^{61}$ $-(CH_2)_nOR^{60}$, $-(CH_2)_nNR^{60}R^{61}$, $-(CH_2)_nSR^{60}$, $-(CH_2)_n$ aryl, $-(CH_2)_n$ heteroaryl, or $-(CH_2)_n$ heterocycloalkyl, wherein n is 1 to 3;

R^4 is H, halo, alkyl or haloalkyl;

R^5 is H, alkyl, halo, or aryl;

R^6, R^7, and R^8 are each independently -NH-Z-aryl or -NH-Z-heteroaryl wherein Z is $C_1 - C_4$ alkyl, alkenyl, or alkynyl; Z optionally having one or more hydroxy, thiol, alkoxy, thioalkoxy, amino, halo, $NR^{60}SO_2R^{61}$ groups; Z optionally incorporating one or more groups selected from the group consisting of CO, CNOH, $CNOR^{60}$, $CNNR^{60}$, $CNNCOR^{60}$ and $CNNSO_2R^{60}$;

R^{60}, R^{61}, R^{62}, and R^{63} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, hydroxy, alkoxy, aryl, heteroaryl, heteroarylalkyl, and alkyl-R^{25};

R^{25} is hydrogen, alkenyl, hydroxy, thiol, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, aryl, heteroaryl, cyano, halo, sulfoxy, sulfonyl, $-NR^{30}COOR^{31}$, $-NR^{30}C(O)R^{31}$, $-NR^{30}SO_2R^{31}$, $-C(O)NR^{30}R^{31}$, heteroaryl or heterocycloalkyl; and

R^{30} and R^{31} are, independently, hydrogen, alkyl, or cycloalkyl.

The substituent definitions of the claimed compounds encompass chemically and biologically distinct groups. Further, the claims literally encompass the treatment of tumors with millions of possible compounds.

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

That factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of

unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain). As illustrative of the state of the art, the examiner cites Sausville *et al.* (Cancer Research, 2006, vol. 66, pages 3351-3354) and Johnson *et al.* (British J. of Cancer, 2001, 84(10):1424-1431).

Sausville *et al.*, cited for evidentiary purposes, teaches that traditionally explored tumor model systems are insufficient to predict how actual human beings will respond to treatment in the clinic (page 3351, left column). Even when drugs with evidence of anticancer activity in preclinical *in vivo* models are given their maximum tolerated dose in humans, they frequently fail to produce useful activity in humans (*id.*). Also, with regard to unpredictability, Johnson *et al.*, also cited for evidentiary purposes, teach that the *in vivo* activity of 39 different agents in a particular histology in a tumor model did

not correlate to activity in the same human cancer. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Further, the mode of action of anticancer agents is often unknown or very unpredictable and administration of such agents is often accompanied by undesirable side effects.

These articles plainly demonstrate that the art of treating cancer, particularly in humans, is extremely unpredictable, particularly in the case of a single compound or genus of compounds being used to treat any and all cancers.

2. The breadth of the claims

The claims are extremely broad insofar as they disclose the general treatment of cancer administering to a mammal an IGF1R inhibitor in combination with an anticancer agent. It is noted that the claimed chemical formulas encompass millions of possible compounds.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for determining the particular administration regimens (*e.g.*, dosages, timing, administration routes, etc.) necessary to treat all of the various cancers claimed, particularly in humans.

The direction concerning treating cancer is found in the specification which only discloses Applicants' intention to do so. There is no evidence of record that any of the claimed compounds actually inhibit tumor growth *in vitro* or *in vivo* and Applicants have

provided no assays for determining the cell growth inhibitory effect of the claimed compounds. It is noted that WO 02/079192 discloses methods of treating cancer with the same compounds as instantly claimed. Even here, however, only 30 of possibly millions of compounds were shown to inhibit the growth of HT-29 colon cancer cells *in vitro*. Even fewer compounds were shown to inhibit the growth of MCF-7 breast cancer cells and Colo205 colon cancer cells (page 32, Table 1).

Since none of the claimed compounds have been shown to inhibit tumor growth in vivo, how is the skilled physician to know what dose to administer to a subject for each of the pathologically different tumors and structurally diverse compounds encompassed by the claims? There are no guidelines for determining the doses needed to treat a colon tumor *vs.* a breast tumor *vs.* a pancreatic tumor *vs*. a prostate tumor. Are the identical doses to be used for treating these unrelated tumors? There are no *in vitro* cellular assays or *in vivo* assays described in the specification, but even if there were, it is unclear if such assays correlate to the clinical treatment of all of the tumors encompassed by the claims. For example, there is no working example of treatment of any tumor in a human subject. Further, it is not apparent that the 30 compounds of WO 02/079192 are representative of the millions of possible structurally diverse compounds encompassed by the present claims.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the full scope of the instantly claimed genera

of compounds could be predictably used as a treatment for all tumors as inferred in the claims and contemplated by the specification. Applicants appear to predicate patentability of their claimed method on the basis that IGF1R inhibitors are non-selective. As such, Applicants propose administering an anticancer agent in combination with the claimed IGF1R inhibitors in order to achieve a synergistic result. Whether any particular IGF1R inhibitor: 1) is effective in treating any given tumor requires individual testing of each IGF1R inhibitor in assays known to correlate to clinical efficacy.

Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

In the instant case, Applicants have presented a general idea that because some compounds of the invention have been shown by others to inhibit cancer cell proliferation in vivo, the millions of possible compounds encompassed by the claims must therefore, *a priori*, be useful in the treatment of tumors when used in combination with an anticancer agent. However, the claims encompass a multitude of compounds (literally millions) having a plethora of chemically and biologically distinct substituents. Accordingly, it would take undue experimentation to determine exactly what compounds encompassed by the claims will have efficacy against any given cancer in a subject.

In this regard, the law requires that disclosure in an application shall inform those skilled in the art how to use Applicant's invention, not how to find out how to use for themselves.

Applicants say that their invention is in the discovery that IGF1R inhibitors with an additional anticancer agent is used to achieve a synergistic result. They are not claiming the compounds *per se*. Whatever the nature of the dosage unit, it may be administered. The "effective dose" as instantly claimed appears to mean that somewhere in the dosage range, an antitumor effect in a subject will be achieved. However, Applicants do not say at what point in the process of administering to a patient, say a 10 mg capsule, an anticancer effect may be expected in the course of proceeding at some unspecified intervals toward a possible 200th capsule for the day (*i.e.*, a total of 2,000 mg for an average human). Nor do the Applicants suggest whether it might be better to start off with a 10 mg capsule, a 50 mg tablet or a 150 mg bolus injection.

This uncertainty, particularly when coupled to the fact that the claims encompass millions of possible compounds, which, in turn, is coupled to the fact that the subject being treated is not necessarily a human being, amounts to a failure to comply with the requirements of 35 U.S.C. 112, 1st Paragraph. In effect, Applicants have said to those skilled in the art: Here is a group of compounds, some of which may inhibit IGF1R and some of which have anticancer activity *in vitro* against three cell lines (as evidenced by WO 02/079192); you can put any of them up in convenient dosage units and you can try them out on human patients or animal subjects as you wish and somewhere along the

line, for any given compound in any given cancer, from a dose of 100 mg/m^2 to 1,000 mg/m^2, you will probably achieve an antitumor effect in a subject, but only *if* the tumor in the patient is IGF1R responsive.

In other words, those skilled in the art, by investigations along the above lines, and by a great amount of work, can eventually find out how to use the Applicants' invention to treat tumors in subjects by administering one of the millions of compounds encompassed by the claims. It is evident that a very small percentage of the claimed compounds have actually been synthesized and tested by Applicants. In other words, there is no guidance provided as to which of the millions of possible compounds might be expected to have antitumor activity *in vivo* as instantly claimed.

Determining if any particular claimed compound would treat any particular cancerous disease state would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it to clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the limited guidance and direction provided by Applicants. Further, as noted *supra*, even *in vitro* and *in vivo* assays do not always correlate to efficacy in humans and are not generally predictive of clinical efficacy.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claims 1, 21, 22, and 26-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an Enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[2]

Attention is directed to In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,

[2] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the art in the assessment of undue experimentation.

1) the nature of the invention; state of the prior art; relative skill of those in the art; and the predictability of the art;

The invention is directed to a method for treating cancer in a mammal. The claimed invention relates to treating a mammalian subject, which encompasses both any animal and any disease. Various diseases having various different causes are not treatable by a single composition. Given the great diversity between various diseases (viral infections, bacterial infection, cancers, autoimmune diseases, clogged arteries, neurological diseases, etc.), the unpredictability of treating an animal (e.g., no specific disease) has a number of facets, as discussed hereinafter.

A. Treatment of Disease Type

While the state of the art is relatively high with regard to the treatment of specific diseases with a specific agent, it is long underdeveloped with regard to the treatment of an animal broadly, that is, general treatment, with no specific disease combined with a specific drug therefore. In particular, there is no known "treatment" drug, that can treat, "all that ails you". This is why the National Cancer Institute (NCI) has the extensive *in vitro* drug-screening program it does. As discussed by the court in In re Brana, 51 F.3d 1560 (Fed. Cir. 1995), *in vitro* assays are used by NCI (such as the P388 and L1210

lymphocytic leukemia tests at issue therein) to measure the potential antitumor properties of a candidate compound. Brana at 1562-63. If success is shown in this initial screening step, this demonstrates that at least one cancer type (e.g., lymphocytic leukemia) is sensitive thereto, and provides the incentive to select it for further studies to determine its usefulness as a chemotherapeutic agent against other cancer types (lung, breast, colon, etc.) *Id.* at 1567-68. These *in vitro* tests are considered reasonably correlative of success *in vivo*.

Thus, a considerable amount of *in vitro* empirical testing is required, with no *a priori* expectation of success being present, before a candidate for even treating a specific disease, such as, breast cancer.

B. The therapeutic agent used

The claims have a long list of therapeutic agents with no correlation to which diseases. Thus, it is unclear, which drug treats which cancer.

2) the breadth of the claims; the scope of the method claims include a method for treating cancer in a mammal. The claims are very broad and inclusive of "treating a mammalian subject" generally, which includes any treatment. Also, the claims are so broad that they do not correlate which drugs treat which ailments.

3) the predictability or unpredictability of the art; the art does not enable a person of ordinary skill in the art to make and use the claimed invention without resorting to undue experimentation. The burden of enabling one skilled in the art to a method for treating all types of cancer in a mammal would be much greater than that enabling the treatment. In the instant case, the specification does not provide guidance as to how

one skilled in the art would accomplish the objective of treating other types of cancer. Nor is there any guidance provided as to a specific protocol to be utilized in order to show the efficacy of the presently claimed active ingredients for treating other types of cancer.

No experimental evidence or mechanism of action for supporting treating all types of cancer using the specified actives by simply administering, by any method, an amount of the claim specified active agents. The specification fails to enable one of ordinary skill in the art to practice the presently claimed method for treating the risk of all types of tumors.

It is unpredictable to practice with a mammalian subject treating for all types of cancer with a chemical administration as instantly claimed. The specification is viewed as lacking an adequate enablement of where all types of cancer may be actually treated.

4) the relative skill of those in the art; the relative skill of those in the art of pharmaceuticals is high.

5) the amount of direction or guidance presented; the specification and the example does not provide any guidance in terms of treating other types of cancer. The specification provides no direction for ascertaining, *a priori*, which diseases can be treated with which drug.

6) the presence or absence of working examples; no working examples are provided for treating all types of cancer with the same compound, for example in a patient, in the specification. The applicant has not provided any competent evidence or

disclosed any tests that are highly predictive for the preventative effects of the instant composition. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

7) the quantity of experimentation necessary; the quantity of experimentation would be an undue burden to one of ordinary skill in the art and amount to the trial and error type of experimentation. Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant process claims. In view of the breadth of the claims, the chemical nature of the invention and unpredictability of treating all types of cancer in a mammal, and the lack of working examples regarding the activity as claimed, one skilled in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims. The lack of adequate guidance from the specification or prior art with regard to the actual treatment fails to rebut the presumption of unpredictability present in this art. Applicants fail to provide the guidance and information required to ascertain which particular disease the claimed agent will be effective against without resorting to undue experimentation. Applicant's limited disclosure of the treatment of is not sufficient to justify claiming all treatment broadly.

In consideration of each of factors 1-7, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by

the present application disclosure, examples, teaching and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

LACK OF WRITTEN DESCRIPTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH:

Claims 27-30 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the instant case, claim 1 recites the limitation "...hydrates, prodrugs and solvates thereof [of compounds of formula I]..." There is insufficient written basis for any hydrates, prodrugs, or solvates of compounds of formula I.

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP §2163. In particular, *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plan for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications under the 35 U.S.C. 112.I "Written Description" Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description

requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function and structure..." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting *Guidelines*, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

Applicant has failed to provide any structural characteristics, chemical formula, name(s) or physical properties of any hydrates, solvates, or prodrugs of compounds of Formula I as recited in the instant claims. In fact, the Examiner is unaware of any such hydrates, solvates, or prodrugs having been made or disclosed in the art. As noted *supra*, the courts have held that the written description requirement requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plan for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566. In the present case, Applicants have disclosed neither a precise definition nor a plan for obtaining any solvates, hydrates, or prodrugs of the claimed compounds.

Claims 21, 22, and 26-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as

to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses chemicals, such as compounds comprising of IGF1R inhibitor, which meet the written description and enablement provisions of 35 USC 112, first paragraph.

However, claims 21, 22, and 26-30 are directed to encompass derivatives, which only correspond in some undefined way to specifically instantly disclosed chemicals. None of these derivatives, meet the written description provision of 35 USC § 112, first paragraph, due to lacking chemical structural information for what they are and chemical structures are highly variant and encompass a myriad of possibilities. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath, Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

With the exception of the above specifically disclosed chemical structures, the skilled artisan cannot envision the detailed chemical structure of the encompassed derivatives, analogs, etc., regardless of the complexity or simplicity of the method of

isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The chemical structure itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> …To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.,* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli,* 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

Therefore, only the above chemically structurally defined chemicals, but not the full breadth of the claim(s) meet the written description provision of 35 USC § 112, first paragraph. The species specifically disclosed are not representative of the genus

because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC § 112 is severable from its enablement provision. (See page 1115).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 27 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of Serial No. 10958869, 10263448, and 10751798.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claim is either anticipated by, or would have been obvious over, the reference claims.

In this case, the claims of the instant application are furthermore drawn to a

method for the synergistic treatment of cancer administering to a mammal in need a therapeutic effective amount of an IGF1R inhibitor in combination with a therapeutically effective amount of an additional anticancer agent. Thus, the pending applications and and the method in the instant application administer the same active combination to the same or overlapping patient population and thus overlap in scope. Accordingly, claim 27 is not patentably distinct over the above mentioned claim in the pending applications.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zohreh Vakili whose telephone number is 571-272-3099. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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March 20, 2008

/Ardin Marschel/

Supervisory Patent Examiner, Art Unit 1614